

ON THE MECHANISM OF REGIOSELECTIVITY CONTROL BY DONOR SUBSTITUENTS ON  
ELECTROPHILIC ALKENES: APPLICATIONS TO QUINONE CYCLOADDITION REGIOSELECTIVITY

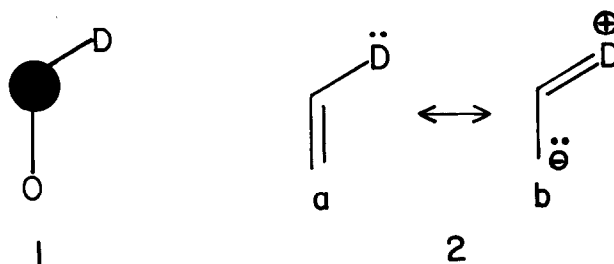
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Summary: Donor substitution on alkenes slightly increases the LUMO coefficient at the site of substitution. However, nucleophiles preferentially attack the unsubstituted terminus of the alkene due to direct repulsive interactions between the nucleophile and the substituent. Secondary orbital interactions make the terminus remote from the site of substitution the most electrophilic. LUMO coefficients, or equivalent spectroscopic measures, esr hyperfine coupling in the esr spectra of radical anions, are appropriate for prediction of reactivities of unsubstituted positions but not substituted ones.

In the preceding Communication, we reported the regioselectivities observed in cycloadditions of nucleophilic dienes to electrophilic quinones made unsymmetrical by methoxy substituents.<sup>2</sup> Although extensive data are available only for methyl and methoxy substituents,<sup>2,3</sup> we propose the following generalization based on these results: electron-donating substituents deactivate alkenes toward attack by nucleophilic cycloaddends (or nucleophiles) and direct attack to the carbon remote from the substituent.

This generalization is contrary to the prediction based purely on alkene LUMO coefficients, which are polarized as shown in an exaggerated fashion in 1.<sup>4</sup> The results also contradict classical resonance theory arguments, which would imply that a donor substituent should cause a buildup of electron-density at the remote carbon, as shown in 2b, resulting in deactivation of this carbon toward attack by nucleophiles. We report here a rationale of these experimental results, and a refinement of frontier molecular orbital theory which is generally applicable to the understanding of nucleophilic addition regioselectivity. We also emphasize that LUMO coefficients alone are still reliable indications of the sites of attack of nucleophiles at unsubstituted positions.



Inspection of frontier orbital coefficients is inadequate for the prediction of regioselectivity, when there is little or no difference between the coefficients at the two termini. This is because an attacking reagent interacts not only at the site of bond formation, but with attached atoms as well, through conventional steric effects, and through secondary orbital interactions.<sup>5</sup> For example, Figure 1 shows the HOMO and LUMO (STO-3G) of methyl vinyl ether, a simple model for a methoxy-substituted dienophile.<sup>6</sup> The site of attack by electrophiles on this species can be rationalized without recourse to

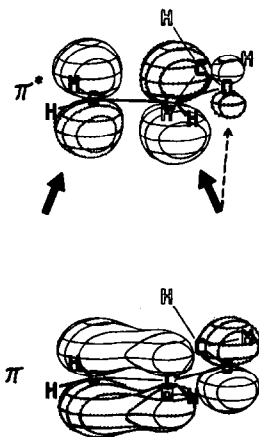


Figure 1. HOMO (bottom) and LUMO (top) of methyl vinyl ether.<sup>6</sup>

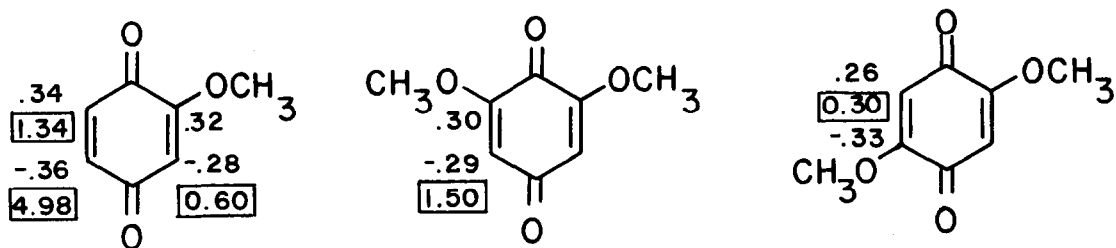
secondary orbital interaction arguments: HOMO polarization is large, and attack of electrophiles at the unsubstituted terminus is favored because charge transfer interactions between the alkene HOMO and the electrophile LUMO are clearly larger at this site. An electrophile approaching the substituted carbon would experience less overlap with the HOMO due to the smaller coefficient at this carbon, but also due to antibonding secondary orbital interactions with the oxygen orbital. In the LUMO, the difference in carbon p orbital coefficient magnitudes is barely perceptible, and can hardly be responsible for the high regioselectivity observed upon attack of nucleophiles or electron-rich dienes on such a species. However, when a nucleophile attacks the methoxy-substituted terminus of an alkene, the HOMO of the nucleophile will experience an antibonding interaction with the oxygen p orbital, represented in Figure 1 by a dotted arrow. Secondary orbital interactions will diminish the net HOMO-LUMO overlap. Such an effect will not occur upon attack of the nucleophile at the unsubstituted terminus. Attack

of the nucleophile still occurs at the terminus with highest effective LUMO density, but this is dictated by secondary orbital interactions rather than by the relative LUMO coefficient magnitudes at the two termini.

Computational tests of these arguments were obtained by ab initio SCF calculations on model systems using the 4-31G basis set.<sup>7</sup> Attack of the model nucleophile, hydride, on the unsubstituted terminus of undistorted methyl vinyl ether is favored by 6 kcal/mol over attack at the substituted terminus ( $r_{C-H}$  was set at  $2\text{\AA}$ ;  $\angle CCH$  was set equal to  $109.5^\circ$ ). At the same computational level, the 1-methoxyethyl anion is 19 kcal/mol less stable than the 2-methoxyethyl anion. That is, forces (such as secondary orbital interactions) present in early transition states steer attack of nucleophiles to the less substituted terminus, in spite of the fact that this mode of attack ultimately produces the thermodynamically less stable ionic product.

While these results clear up a series of anomalies discovered for nucleophilic attack on donor-substituted quinones, they confuse the explanation of results obtained by Fleming and coworkers for Diels-Alder reactions of unsymmetrical electron-rich dienes with electron-rich alkenes.<sup>8</sup> These workers found that the *meta* orientation predicted<sup>4</sup> for such a reaction was observed, but with very low regioselectivity, indicative of a preference of several tenths of a kcal/mol for one regioisomer. The general prediction of low regioselectivity in such reactions still emerges "triumphant",<sup>9</sup> although somewhat less smashingly so.

Returning to the general case of nucleophilic attack on electrophilic alkenes, the secondary orbital effect operates only upon attack at the substituted carbon, so that the relative facility of attack at the various unsubstituted carbons of benzoquinones are still predictable from the LUMO coefficients of the quinone. Figure 2 shows the STO-3G LUMO coefficients of methoxybenzoquinones and two dimethoxybenzoquinones. For comparison, the hyperfine splittings,  $a_H$ , are shown also, in boxes.<sup>10-12</sup> Neglecting the substituted



position, methoxybenzoquinone has the LUMO coefficients and hyperfine coupling in the order  $C_5 > C_6 > C_3$ . A variety of evidence indicates that reactivities of these positions toward nucleophiles, or toward the more nucleophilic termini of dienes, also follows this order.<sup>13</sup> For the dimethoxybenzoquinones, the decrease in reactivity observed in cycloadditions<sup>2</sup> also correlates with the decrease in LUMO coefficient magnitudes at the unsubstituted carbons.

Although frontier orbital coefficients account well for the reactivities of unsubstituted positions, it is now apparent that it is necessary to consider direct interactions between MOs of attacking reagents and of substituents in order to quantitate reactivities of substituted positions.

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#### References and Notes

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